Exhibit 1

(SNS)

The sympathetic nervous system plays a major role in the development and progression of congestive heart failure (CHF). The hyperactivity of the SNS contributes to the development of significant and life-threatening cardiac arrhythmias such as ventricular fibrillation. More recent studies have suggested that the overactive SNS contributes to the negative morphologic changes in the heart (ventricular hypertrophy, increased myocardial fibrosis, Cardiomyocyte apoptosis) of patients with CHF. Patients with CHF exhibit plasma norepinephrine concentrations which are greatly increased relative to normal patients. In fact, plasma norepinephrine (NE) has been shown to be positively correlated with patient prognosis (i.e., high plasma NE, poor prognosis).

In light of the hyperactive SNS, pharmacological interventions have been used to mitigate these deleterious effects in CHF patients. The strategy which has been investigated most and has been accepted as a useful clinical tool in the management of CHF is the use of β-adrenergic receptor antagonists such as propranolol, metoprolol and carvedilol.

To Page No. 1

Witnessed & Understood by me. Date

Invented by Date

Recorded by

These agents have proven useful in reducing the morbidity & mortality associated with CHF when administered clinically.

What is proposed in the invention described herein is a method of treating CHF by the administration of clonidine via an intraspinal route (i.e., epidural or intrathecal). Clonidine is an imidazoline which interacts with pre and post-junctional α_2-adrenergic receptors. Clonidine is a receptor agonist which binds to the receptor (normally) and activates it. In nerve cells this typically produces hyperpolarization by activating K+ channels or inhibits neurotransmitter release by antagonizing Ca++ channels. ~~activation by endogenous neurotransmitters (i.e. NE).~~ The ability of clonidine to decrease sympathetic outflow has been known for sometime and is believed to be mediated via α_2 adrenergic receptors in the brain stem (specifically the nucleus tractus solitarius). An appreciation of this clonidine-mediated decrease in sympathetic outflow has lead several investigators to evaluate the effects of clonidine for the treatment of CHF (Azevedo et al, 1999 J. Am Coll Cardiol. 33(1): 186-91; Esler and Kaye, 1998 J. Auton. Nerv. Sys. 72(2-3): 210-9; Manolis et al, 1998 Clin Exp

To Page No. 11

Witnessed & Understood by me, Date Invented by Date
Recorded by

From Page No. 2

Hypertens 20(7): 717-31; Zhang et al, 1998 Int. J. Cardiol. 65(3):233; Girgis et al, 1998 Am J Cardiol 82(3)335-7, Yan-hua et al, 1997 Int J Cardiol 59(2): 139-44). Large, multicenter, randomized, controlled prospective studies evaluating the effect of oral, transdermal or any other form of clonidine administration for the treatment of CHF have yet to be performed. This is in contrast to the use of β-adrenergic blockers for CHF which have been evaluated extensively and have been found to be clinically useful for CHF. Treatment of CHF with clonidine vs. a β-adrenergic antagonist may provide several clinically significant advantages. In general, the pharmacologic mechanism of clonidine vs the β-blockers would appear to be a much more direct and efficient strategy for dealing with the primary clinical problem - excessive sympathetic output. Clonidine via central and peripheral actions decreases the output (NE) of sympathetic nerves (Ⓐ in Figure 1). β-blockers, on the other hand, produce a sympatholytic effect by blocking receptors upon which NE acts. (See Ⓑ in figure

Figure 1

To Page No. 12

Witnessed & Understood by me, Date

Invented by Date

Recorded by

From Page No. 11

Clonidine leads to a rapid and sustained decrease in the release of NE. With β-blockers, NE continues to be released and in fact may be released more in an effort to compensate for the blocked receptors. In addition, β-blockers ~~present only one by~~ affect only some receptors at which NE may act (namely β_1-adrenoceptors) whereas clonidine, by preventing NE release, should produce a much broader therapeutic effect (α_1 and α_2 effects, β_1, β_2, and β_3). Elevated NE which is not directly affected by β-blocker therapy may also produce nonselective effects at various other receptors or other biochemical pathways which may not be well understood (e.g. high concentrations of NE induce apoptosis of myocardial cells in culture). β-blockers are specific for β-receptors whereas clonidine prevents output of sympathetic neurotransmitters. Although NE is the classical neurotransmitter released from sympathetic nerve terminals, it is not the only neurotransmitter released. Peptidergic neurotransmitters such as somatostatin and neuropeptide Y are often colocalized and released from sympathetic nerves. These other neurotransmitters

To Page No. 1

Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by	

From Page No. 12

or neuromodulators that are co-released with NE may play a significant role in the pathogenesis of CHF associated with sympathetic overdrive. β-blockers do not affect these neurochemical pathways whereas clonidine would by presynaptic inhibition of NE and colocalized transmitters. Although β-blockers have been shown to decrease morbidity and mortality associated with CHF, many CHF patients cannot tolerate them. Because β-blockers are negative inotropes, the cardiac output which is already bad in CHF patients may be worsened. Clonidine (especially intrathecal clonidine) may be slowly titrated to decrease sympathetic outflow while preserving cardiac output.

Intrathecal or intracerebroventricular clonidine may provide several advantages over parenteral or oral clonidine. The site of action of where clonidine decreases sympathetic outflow is the brain stem. By delivering directly to the CNS, it may be possible to produce greater efficacy, more controlled drug levels and consistent drug levels at the target site, and decreased side effects. One troublesome side effect associated with oral clonidine is activation of vascular smooth muscle To Page No. 13

Witnessed & Understood by me, Date Invented by Date

Recorded by

From Page No. 13

α_2-adrenergic receptors. This leads to vasoconstriction and increased vascular resistance which is undesirable in CHF patients. This peripheral effect could be avoided or minimized with intrathecal delivery. Another effect of clonidine is increased parasympathetic outflow. By administering intrathecal clonidine, it may be possible to achieve a greater vagal output which would also provide a therapeutic advantage in CHF patients.

In addition to clonidine for which the largest body of data relative to intrathecal infusion exists, other α_2-adrenergic agonists may prove useful for intrathecal treatment of CHF. Such agents include lidamidine, xylazine, methyldopa, guanabenz, para-aminoclonidine, guanfacine, detomidine, medetomidine, and dexmedetomidine, and tizanidine.

To Page No.

Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by	